

Claims:

1. A process for the preparation of racemic diol free base and/or acid addition salt and/or *R*- or *S*-diol free base and/or acid addition salt comprising a separation of an initial non-racemic mixture of *R*- and *S*-diol free base and/or acid addition salt with more than 50% of one of the enantiomers into a fraction being enriched with *S*-diol or *R*-diol free base and/or acid addition salt and a fraction comprising *RS*-diol free base and/or acid addition salt wherein the ratio of *R*-diol:*S*-diol is equal to 1:1 or closer to 1:1 than in the initial mixture of *R*- and *S*-diol **characterized in that**
- i) *RS*-diol free base and/or acid addition salt is precipitated from a solution of the initial non-racemic mixture of *R*- and *S*-diol free base and/or acid addition salt; or
- R*- or *S*-diol free base and/or acid addition salt is dissolved into a solvent from the initial non-racemic mixture of *R*- and *S*-diol free base and/or acid addition salt in said solvent, leaving a residue comprising *RS*-diol free base and/or acid addition salt;
- ii) the residue/precipitate formed is separated from the final solution phase;
- iia) if the residue/precipitate is crystalline it is optionally recrystallised one or more times to form racemic diol;
- iib) if the residue/precipitate is not crystalline, steps i) and ii) are optionally repeated until a crystalline residue/precipitate is obtained and the crystalline residue/precipitate is optionally recrystallised one or more times to form racemic diol;
- iii) the final solution phase is optionally subjected to further purification and *S*-diol or *R*-diol free base and/or acid addition salt is isolated from the final solution phase ;

- iv) the free bases of the diols obtained are optionally converted to acid addition salts thereof or acid addition salts of the diols obtained are optionally converted to other acid addition salts or acid addition salts of the diols obtained are optionally converted to the corresponding free bases.

2. A process according to claim 1 for the preparation of *S*-diol or *R*-diol free base and/or acid addition salt **characterized in that**

- i) *RS*-diol free base and/or acid addition salt is precipitated from a solution of the initial non-racemic mixture of *R*- and *S*-diol free base and/or acid addition salt; or
R- or *S*-diol free base and/or acid addition salt is dissolved into a solvent from the initial non-racemic mixture of *R*- and *S*-diol free base and/or acid addition salt in said solvent, leaving a residue comprising *RS*-diol free base and/or acid addition salt;
- ii) the residue/precipitate formed is separated from the final solution phase, and
- iii) the final solution phase is optionally subjected to further purification and *S*-diol or *R*-diol free base and/or acid addition salt is isolated from the final solution phase.

3. A process according to claim 2 wherein the diol prepared is the *S*-diol free base and/or acid addition salt.

4. A process according to claim 2 wherein the diol prepared is the *R*-diol free base and/or acid addition salt.

5. A process according to claim 1 for the preparation of racemic diol free base and/or acid addition salt **characterized in that**

- i) *RS*-diol free base and/or acid addition salt is precipitated from a solution of the initial non-racemic mixture of *R*- and *S*-diol free base and/or acid addition salt; or
- 5 *R*- or *S*-diol is dissolved into a solvent from the initial non-racemic mixture of *R*- and *S*-diol free base and/or acid addition salt in said solvent, leaving a residue comprising *RS*-diol free base and/or acid addition salt;
- 10 ii) the residue/precipitate formed is separated from the final solution phase,
- 15 iia) if the residue/precipitate is crystalline it is optionally recrystallised one or more times to form racemic diol;
- iib) if the residue/precipitate is not crystalline, steps i) and ii) are repeated until a crystalline residue/precipitate is obtained and the crystalline residue/precipitate is optionally recrystallised one or more times to form racemic diol.
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6. The process according to any one of claims 1-5 wherein the initial non-racemic mixture of *R*- and *S*- diol free base and/or acid addition salt with more than 50% of one of the enantiomers contains more than 50% of *S*-diol, more preferred more than 70% of *S*-diol or most preferred more than 90% of *S*-diol.
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7. The process according to any one of claims 1-5 wherein the initial non-racemic mixture of *R*- and *S*- diol free base and/or acid addition salt with more than 50% of one of the enantiomers contains more than 50% of *R*-diol, more preferred more than 70% of *R*-diol or most preferred more than 90% of *R*-diol.
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8. The process according to any one of claims 1-7, wherein the ratio of *R*-diol:*S*-diol in the *RS*-diol of the residue/precipitate is 0.5:1.5 or 0.9:1.1 or 0.95:1.05 or 0.99:1.01 or 0.98:1.02 or preferably 1:1.

9. The process according to any one of claims 1-8 wherein the *RS*-diol comprised in the residue/precipitate is in the form of a free base and/or an acid addition salt thereof; and independently thereof the *R*- or *S*-diol comprised in the final solution phase is in form of a free base and/or as an acid addition salt thereof.
- 5 10. The process according to any one of claims 1-9 wherein *RS*-diol free base and/or acid addition salt is precipitated from a solution of the initial non-racemic mixture of *R*- and *S*-diol free base and/or acid addition salt.
- 10 11. The process according to any one of claims 1-10 wherein the acid used for precipitating *RS*-diol as a salt in step i) is an acid which precipitates a mixture of the *R*- and *S*-enantiomers and leaves the mother liquor enriched with either the *S*- or *R*-enantiomer of the diol free base and/or acid addition salt.
- 15 12. The process according to claim 11 wherein the acid may be:
- added after the initial non-racemic mixture of *R*- and *S*-diol free base and/or acid addition salt is obtained or dissolved in a suitable solvent; and/or
 - present in the solvent during and/or prior to dissolution of the initial non-racemic mixture of *R*- and *S*-diol free base and/or acid addition salt; and/or
 - present in the initial non-racemic mixture of *R*- and *S*-diol free base and/or acid addition salt during and/or prior to dissolution in the solvent.
- 20 13. The process according to any one of claims 1-9 wherein *R*- or *S*-diol free base and/or acid addition salt is dissolved into a solvent from the initial non-racemic mixture of *R*- and/or *S*-diol free base and/or acid addition salt in said solvent, leaving a residue comprising *RS*-diol free base and/or acid addition salt.
- 25 14. The process according to any one of claims 1-9 and 13 wherein the acidic part of the *RS*-diol acid addition salt comprised in the residue formed in step i) is an acid which allows the selective dissolution of either *R*- or *S*-diol free base
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and/or acid addition salt and leaves the undissolved material enriched with the *RS*-diol acid addition salt.

15. The process according to claim 13 wherein the acid may be:
- 5 • present in the solvent before the initial non-racemic mixture of *R*- and *S*-diol free base and/or acid addition salt is mixed with the solvent; and/or
 - mixed with the solvent together with the initial non-racemic mixture of *R*- and *S*-diol free base and/or acid addition salt; and/or
 - 10 • mixed with the solvent after the initial non-racemic mixture of *R*- and *S*-diol free base and/or acid addition salt is mixed with the solvent; and/or
 - present in the initial non-racemic mixture of *R*- and *S*-diol free base and/or acid addition salt during and/or prior to the mixing with the solvent.
16. A method according to claims 1-15 wherein the *RS*-diol acid addition salt is
- 15 obtained from the initial non-racemic mixture of *R*- and *S*-diol free base and/or acid addition salt in a solvent selected from the group consisting of toluene, ethylacetate, diethylether, THF, water, alcohols such as *iso*-propylalcohol, acetonitrile, and ketones such as acetone and methyl isobutyl ketone; or mixtures thereof.
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17. The process according to any one of claims 1-16 wherein the acid used in step i) is HCl, HBr, H₂SO₄, *p*-toluenesulfonic acid, methanesulfonic acid, acetic acid or oxalic acid.
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18. The process according to claim 17 wherein the the acid used in step i) is HCl, HBr, or oxalic acid; thereby a hydrobromide salt, hydrochloride salt or oxalate salt of the *RS*-diol is formed, preferably in crystalline form.
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19. The process according to any one of claims 1-18, wherein 0.2-10 mol of acid may be used, such as 0.2-0.4 mol, or 0.4-0.6 mol, or 0.9-1.1 mol or 1.8-2.2 mol of acid is used for each mol of *S*- and *R*-diol comprised in the initial non-racemic mixture of *R*- and *S*-diol free base and/or acid addition salt.

20. The process according to any one of claims 1-18, wherein 0.3-4.0 mol, such as 0.4-0.6 mol, or 0.9-1.1 mol or 1.8-2.2 mol of acid is used for each mol of *RS*-diol comprised in the residue/precipitate.
- 5 21. The process according to any one of claims 1-10 and 13 wherein a free base of the *RS*-diol is obtained in step i), preferably in crystalline form.
- 10 22. A method according to any one of claims 1-10, 13 and 21 wherein the *RS*-diol free base is obtained from the initial non-racemic mixture of *R*- and *S*-diols in a solvent selected from the group consisting of alkanes such as heptane or hexane, aromatic hydrocarbons such as toluene, benzene and xylene, polar solvents such as acetonitrile, alcohols such as methanol and iso-propylalcohol and ketones such as methyl isobutyl ketone; or mixtures thereof.
- 15 23. The process according to any one of claims 1-22 wherein the final solution phase is subjected to one or more further separations of *RS*-diol as described under steps i) and ii) before isolation of the *S*-diol or (*R*-diol) from the final solution phase.
- 20 24. The process according to any one of claims 1-4 and 6-23 wherein the *S*-diol (or *R*-diol) is isolated from the final solution phase by evaporation of the solvent.
- 25 25. The process according to any one of claims 1-4 and 6-24 wherein the final solution phase is acidic and the *S*-diol (or *R*-diol) is isolated from the final solution phase by basifying the final solution phase, followed by phase separation or extraction with a solvent followed by evaporation of the solvent.
- 30 26. The process according to any one of claims 1-4 and 6-24, wherein *S*-diol (or *R*-diol) free base and/or acid addition salt is isolated from the final solution phase by precipitation of the *R*- or *S*-diol free base and/or acid addition salt; suitably a phosphate salt or an oxalate salt of *R*- or *S*-diol is precipitated.

27. The process according to any one of claims 1-4 and 6-26 wherein the *S*-diol (or *R*-diol) obtained contains a minor amount of the opposite enantiomer such as less than 3%, more preferred less than 2%, or most preferred less than 1%.

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28. Use of the *RS*-diol free base and/or acid addition salt and/or *S*-diol free base and/or acid addition salt and/or *R*-diol free base and/or acid addition salt prepared according to any one of claims 1-27 for the preparation of citalopram free base and/or acid addition salt and/or *R*-citalopram free base and/or acid addition salt and/or *S*-citalopram free base and/or acid addition salt.

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29. A method for the preparation of citalopram free base and/or as acid addition salt and/or *S*-citalopram free base and/or as acid addition salt and/or *R*-citalopram free base and/or as acid addition salt comprising preparation of *RS*-diol free base and/or as acid addition salt and/or *S*-diol free base and/or as acid addition salt and/or *R*-diol free base and/or as acid addition salt according to any of claims 1-27 followed by ring closure.

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